Title: Physical activity, exercise and rheumatoid arthritis: effectiveness, mechanisms and implementation

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Practice Points

- Rheumatoid arthritis is characterised by symptoms and functional limitations that can interfere with regular engagement in physical activity. It is also associated with systemic manifestations, most notably cardiovascular disease.
- The cost of rheumatoid arthritis is proportionately higher than this of other non-communicable diseases.
- Physical activity and exercise are safe and effective interventions to ameliorate symptoms and systemic manifestations of rheumatoid arthritis.
- Implementation of physical activity interventions in clinical practice remains extremely limited; it should be led – in a pragmatic manner – by rheumatology healthcare practitioners and supported by social innovation.

Abstract

Rheumatoid arthritis is characterised by functional disability, pain, fatigue and body composition alterations that can further impact upon physical function. It is also associated with systemic manifestations, most notably an increased risk for cardiovascular disease. There is strong evidence to suggest that increasing physical activity and/or exercise can simultaneously improve symptoms and reduce the impact of systemic manifestations of RA. However, implementation of interventions to facilitate increased physical activity and/or exercise within routine clinical practice is slow, due to patient-specific and healthcare professional-related barriers but also due to lack of relevant infrastructure and provision. We review the evidence supporting the physiological adaptations and beneficial effects occurring as a result of increased physical activity and/or exercise in RA and propose an implementation model for facilitating the long-term engagement of RA patients. We propose that implementation should be led, in a pragmatic manner, by rheumatology healthcare practitioners and supported by social innovation.

1.0 Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease, typically presenting as symmetrical polyarthritis of proximal small and other synovial joints. It affects approximately 1% of the adult general population and it is accompanied by symptoms – such as pain, stiffness, swelling and fatigue – that may have debilitating effects on the functional ability and quality of life of affected patients. In addition, RA is accompanied by systemic manifestations, most notably an increased risk for cardiovascular disease (CVD) as well as detrimental changes in body composition, favouring increased fat mass deposition and reduced muscle mass [a condition termed "rheumatoid cachexia"(1)]. These, in turn, further deteriorate function and the ability to perform daily tasks (1). Therefore, it is not surprising that almost a third of RA patients become unemployed as a result of their condition (2) and have 10 times the work disability rate compared to the general population (3). The introduction of early, intensive anti-inflammatory / immuno-modulating treatments and strategies involving conventional synthetic and biologic disease-modifying anti-rheumatic drugs (DMARDs) and more recently newer small molecules, has significantly improved the outcome of these patients but, thus far, without substantial changes to their employment ability and with a significant increase (around 300%) of the direct healthcare costs (3). As such, identifying beneficial, sustainable and cost-effective interventions that may alleviate the burden of RA for the individual, healthcare services and society as a whole should be adopted and implemented as part of routine clinical practice.

An intervention that can improve both disease-related as well as systemic manifestations in RA, reducing at the same time the overall cost associated with the disease, is an increase in physical activity. Physical activity, is any bodily movement that increases energy expenditure above resting levels, such as walking and gardening. Exercise on the other hand, is a mode of physical activity that is planned, structured and repetitive, such as swimming three times per week.

Over the last two decades, good quality evidence has accumulated, clearly demonstrating that increasing physical activity is a behavior that can significantly improve many different disease-related (e.g. fatigue, functional disability, inflammation) and systemic outcomes (e.g. CVD risk and body composition) as well as impact beneficially on RA costs. Specifically, in terms of cost, increased physical activity in RA associates with a reduced number of hospital admissions and days of hospitalization (4); this is also confirmed in patients with CVD where increasing physical activity through cardiac rehabilitation, is both an effective and cost-effective intervention for reducing national healthcare costs (5). For health outcomes in RA, we and others have shown in systematic reviews (two published by the Cochrane Collaboration), that increased physical activity results in significant improvements in functional ability, cardiorespiratory fitness and strength (6-8), cardiovascular health (9) and fatigue (10). Moreover, randomized and controlled clinical trials consistently demonstrate significant reductions of radiological damage in small and large joints, as a result of increased levels of physical activity participation (11-14), as well as reduced CVD risk and beneficial body composition changes that can reverse rheumatoid cachexia (14-17). It is important to note that, increasing physical activity or engaging in different types of exercise, even in high-intensity exercise, is safe in RA with no studies reporting any adverse effects (18); in contrast, a sedentary lifestyle in RA can further promote the increased risk for future development of CVD (19-21).

Despite this well-described cumulative evidence about its beneficial effects, methods to improve physical activity levels in patients with RA are not incorporated in routine clinical care. RA patients, as a result, still remain physically inactive, with activity levels well below those recommended (22), while their cardiorespiratory fitness – a factor that demonstrates very strong associations with all-cause and cardiovascular mortality (23) – is still alarmingly low (24).

2.0 Physiological effects of physical activity on RA symptoms and systemic manifestations

Physical activity is a stimulus that results in significant functional and structural adaptations in different physiological systems, that in turn, may beneficially impact on the overall RA symptomatology. The benefit of increasing physical activity and exercising, is that it can simultaneously improve different physiological mechanisms, which with regards to RA, can benefit two main categories of outcomes for RA sufferers: disease-related symptoms and systemic manifestations.

2.1 Mechanisms mediating the beneficial effects of physical activity on RA symptoms

2.1.1 Inflammation

An area that has received significant research attention in the last few years, is the anti-inflammatory effects of physical activity. Exercise, a part of physical activity, is now considered a major stimulus that can result in anti-inflammatory effects. Exercise can induce both acute and long-term beneficial reductions of the inflammatory response in a dose-dependent manner (i.e. higher exercise intensities will result in more pronounced beneficial effects), via potentially different physiological mechanisms.

The acute phase response depends on a vicious cycle that is based on the co-existence and cross-talk of pro-inflammatory cytokines, predominantly interleukins 1 and 6 (IL-1 and IL-6) and tumour necrosis factor alpha (TNFα). The kinetics of these inflammatory mediators, which are highly expressed in autoimmune diseases including RA, are different during exercise vs. sepsis / inflammation. Specifically, exercise-induced increases in IL-6 do not seem to promote an inflammatory state; instead, exercise-induced increases in IL-6 mRNA expression are thought to act as a trigger for increasing hepatic glucogenolysis and lipolysis, in order to provide more energy for the exercising muscles (25). IL-1 and TNFα remain suppressed during a bout of exercise, while in contrast they are highly overexpressed in sepsis and/or inflammation (25). In support of this, macrophage (inflammation-induced) and intramuscular (exercise-induced) induction of IL-6, depend on different signalling pathways. Inflammation, which is based on IL-6 macrophage signalling, depends on the upstream and downstream signalling of IL-6, induced by the activation of nuclear factor-kB (NF-kB) and necessitates the presence of TNFα (26). In contrast, exercise-induced overexpression of IL-6 occurs without an *a priori* overexpression of TNFα or NF-kB activation, and is regulated by an interaction between the nuclear factor of activated T-cells and glycogen-p38 mitogen activated protein kinase pathways (27). At the same time, exercise-induced increases in IL-6 coincide with increases in the anti-inflammatory cytokines, IL-10, soluble TNF receptor and IL-1 receptor antagonist (25). Thus, an acute bout of exercise, can induce an anti-inflammatory phenotype.

In the longer term, the anti-inflammatory effects of exercise are mainly based on its beneficial effects on body composition. Overweight and obese individuals demonstrate higher inflammatory load, compared to the healthy population while it has been observed that inflammatory processes are activated early in adiposity expansion and progression (28).

Indeed, obesity is now considered an inflammatory condition. The most recent systematic review and meta-analysis on the effects of exercise vs. hypocaloric diets on adiposity, revealed that exercise can result in a greater loss of visceral fat in the absence of weight loss (29). Reducing the size of adipocytes as a result of exercise, results in lower levels of inflammation, even in populations with non-communicable, low-grade inflammatory diseases such as diabetes (30). It is therefore thought that the long-term anti-inflammatory effects of exercise are mainly due to reduction of the size of adipocytes.

2.1.2 Functional ability and fatigue

There is growing evidence that physical activity and/or exercise can significantly improve disease activity and severity in RA patients, facilitating significant improvements in their functional ability and quality of life. Perhaps the most comprehensive randomised controlled trial, the “rheumatoid arthritis patients in training” study, revealed that a two-year high intensity exercise program of combined aerobic and strength training significantly improved functional ability of the exercising RA patients vs. non exercising RA controls; at the same time, high-intensity exercise did not increase radiological damage in the large joints (11). These results are in line with other, smaller randomised controlled trials in this field (31). A 2009 systematic review and meta-analysis of eight studies in the Cochrane Library, which unfortunately has not been updated since, revealed that fitness and strength are significantly improved as a result of exercise training in RA patients, a fact that may explain the significant benefits the patients experience in their functional ability (6). The same review suggests that exercise may also reduce pain in RA. A more recent 2012 unmbrella review of systematic reviews and meta-analyses (both Cochrane and non-Cochrane) revealed that the effect estimates for the efficacy of exercise therapy are generally smaller in RA compared to other musculoskeletal conditions (i.e. osteoarthritis, low back and shoulder pain and fibromyalgia) for improving pain and functional ability (32). Moreover, despite that RA patients may be at increased risk for falling, a 2010 Cochrane Collaboration systematic review concluded that no studies exist in the literature that address physical activity in relation to this particular outcome in RA (33). Finally, a 2010 meta-analysis of randomised controlled trials (10 studies with 547 participants), concluded that resistance exercise training can improve different strength outcomes (isokinetic, isometric and grip strength) (8) which may have a potentially beneficial impact on functional ability and as a result, performance in daily tasks. However, the quality of the studies included in this meta-analysis was evaluated using earlier research quality tools, and thus, the interpretation of these findings should be treated with caution. It seems apparent from the above that: a) the existing meta-analysis need updating as more recent trials has been published from 2010 until 2019 and b) more studies are required in this field to draw definitive conclusions.

The effects of exercise programs on fatigue have also attracted attention in recent studies, since fatigue is a very commonly reported and debilitating symptom of RA. The most recent meta-analysis of five randomised controlled trials reveals that exercising for 12 weeks vs. no exercise, results in significant reductions in fatigue in RA patients. This is an interesting finding, since fatigue is reported by RA patients to be one of the main barriers for non-participation in exercise programs (34), and poses significant questions with regards to the best ways to “convince” people with RA to participate and remain in an exercise programme and how to achieve large scale implementation of such programmes.

2.2 Mechanisms mediating the beneficial effects of physical activity on RA systemic manifestations

2.2.1 Cardiovascular disease

Physical activity has been proposed as a key intervention for reducing the most predominant risk factors for developing CVD, namely insulin resistance, hypertension and hypercholesterolemia. Recent studies confirm that these beneficial effects are also evident in RA. The updated European League Against Rheumatism (EULAR) guidelines acknowledge these issues and have updated their guidelines to recommend lifestyle change for reducing the CVD burden in RA, by including suggestions to increase physical activity (35).

For insulin resistance, exercise enhances the translocation of the insulin-mediated glucose transporter type 4 (insulin regulated glucose transporter) to the sarcolemma which may result in increased glucose uptake in the cell, up to 24 hours post-exercise (36). This transient exercise-induced change in the translocation of insulin-mediated glucose transporter type 4 is thought to be the main mechanism resulting in a long-term improvement in glucose homeostasis in individuals with an insulin resistant phenotype. As such, it comes as no surprise that the most recent Cochrane Library meta-analysis reported that diabetics in exercise interventions (both aerobic and resistance training) had statistically and clinically significantly improved glycemic control when compared to their non-exercising counterparts (37). In RA, both higher physical activity and fitness (i.e. maximal oxygen uptake) levels have been associated with reduced insulin resistance (24, 38), although the mechanisms have not been studied in detail in this population. Potentially the combination of increased physical activity and anti-TNFα therapy may hold great promise in improving insulin sensitivity, particularly in normal weight RA, since anti-TNFα therapy seems to reduce insulin resistance (39). Overall, insulin sensitivity is impaired with increasing body mass index in RA (40), a phenomenon that can be partly improved via engaging in physical activity.

Elevated blood pressure is also a CVD risk factor that can be reduced by a clinically significant magnitude when physical activity in increased (41). Immediately post-exercise, there is a reduction in blood pressure thought to be caused by reduced peripheral vascular resistance (41, 42). In the longer-term, exercise affects blood pressure via a variety of different mechanisms including enhanced baroreceptor sensitivity, reduced peripheral vascular resistance, improved endothelial function and vasodilator, such as nitric oxide bioavailability, and improved resistance to oxidative stress (42). Findings specifically in patients with RA are well in line with these, although again the mechanisms have not been specifically studied in this population. RA patients with higher physical activity levels as well as higher maximal oxygen uptake have lower blood pressure, when compared to RA patients with lower levels of physical activity or fitness (24, 38).

Various modes of exercise also have beneficial effects on lipoprotein profiles. Exercise-induced changes in lipid profiles are achieved in lecithin-cholesterol acyltransferase, which is an enzyme that converts cholesterol into cholesteryl ester, eventually facilitating synthesis of the anti-atherogenic high-density lipoprotein (43). Furthermore, exercise induces increases in lipoprotein lipase (44), another enzyme with a major role in hydrolysing triglycerides into free fatty acids and glycerol. With regards to the effects of exercise on the major lipoproteins involved in atherosclerosis, a recent review of 15 studies (13 experimental studies and two reviews), confirms that exercise has beneficial effects on lipid profile in both healthy individuals as well as those with hypercholesterolemia (45). Participating in regular exercise can increase high-density lipoprotein while at the same time offsetting relevant increases in triglycerides as well as low-density lipoprotein in atherosclerosis (45). Another meta-analysis of 49 randomized controlled trials in healthy men and women older than 18 years of age with elevated cholesterol, demonstrated that aerobic exercise improves significantly total cholesterol, high-density lipoprotein and triglycerides, while for low-density lipoprotein a beneficial non-significant trend was observed (46). A separate meta-analysis by the same group of authors, confirms these beneficial exercise-induced effects on lipids in women (47), something that may be particularly relevant in a predominantly female population such as this suffering from RA. Studies specifically in RA demonstrate that more physically active patients as well as those with higher levels of cardiorespiratory fitness have significantly better lipid profiles compared to those that have lower physical activity and fitness levels (24, 38), however again the exact mechanisms that may explain such associations in this population have not been studied.

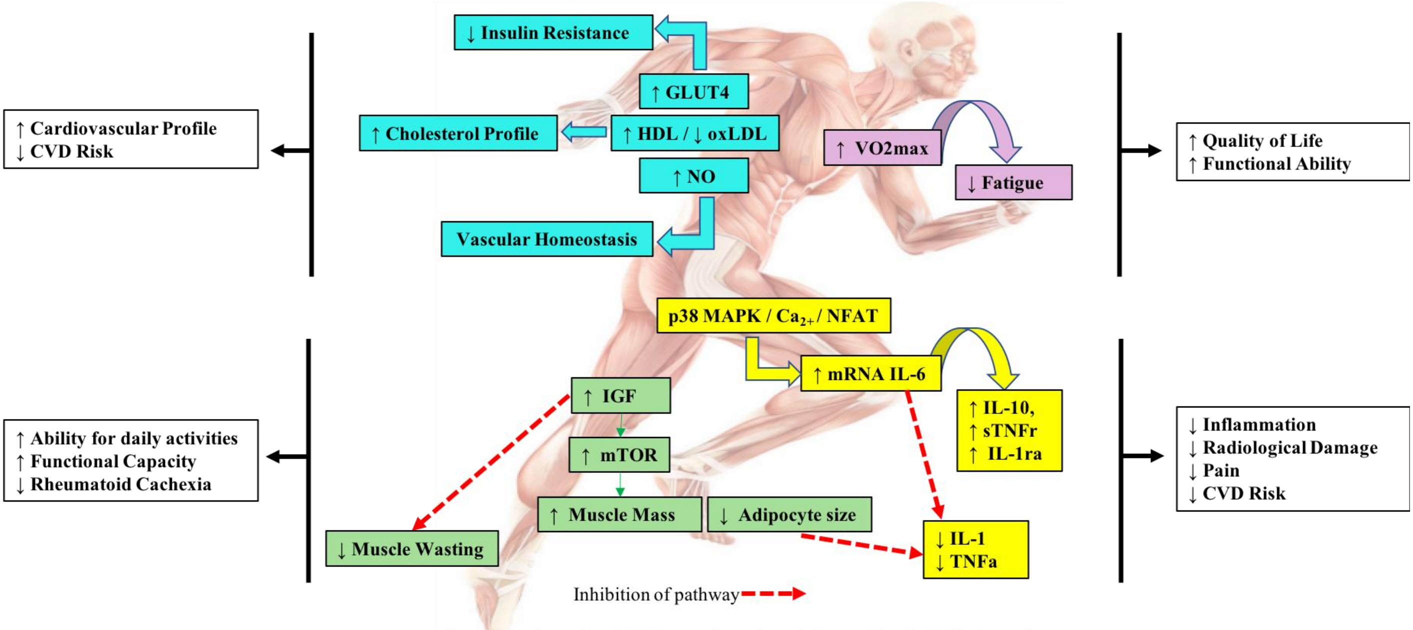
Several other exercise-induced effects may be of relevance in lowering CVD risk. The leading cause of CVD, atherosclerosis, can be beneficially managed via increasing physical activity and fitness levels. A key step in the evolution of atherosclerosis is the oxidization of low-density (LDL) lipoprotein in the endothelium. Increasing cardiorespiratory fitness levels, via appropriately designed exercise interventions, significantly reduces oxidized LDL (48). Moreover, high-intensity exercise training does not enhance oxidative stress processes in RA patients while in the long term, three-nitrotyrosine (a biomarker of nitrogen free radical species modified proteins) significantly reduces, supporting the findings seen in healthy populations that exercise counteracts the development of oxidative stress related mechanisms (49). Finally, significant alterations take place, via exercise, in vascular function. Increasing shear stress due to exercise-induced haemodynamics, results in functional and structural changes in the vasculature, that help reverse CVD processes. Vascular function may be significantly impaired as a result of persistent inflammation in RA (50). In contrast, exercise training for three or six months at intensities of up to 75% of maximum heart rate can significantly improve micro- and macro- vascular function in RA, possibly via the effects of exercise to increase nitric oxide bio-availability, a key mediator for the maintenance of vascular homeostasis (13, 51).

2.2.2 Rheumatoid Cachexia

Rheumatoid cachexia is a condition predominantly driven by the overexpression of TNFα [i.e. a similar pathway with cancer cachexia (52)] and characterised by increased resting metabolic demands (1, 53). This phenomenon can be further deteriorate via smoking (54). This eventually results in significant alterations in body composition of RA patients, characterised by increased fat deposition and reduced muscle mass compared to healthy age- and gender- matched adults (1). Indeed it has been suggested that the body mass index cut-off points for RA patients should be altered for overweight and obesity to 23 kg/m^2 (rather than 25 kg/m^2) and 28 kg/m^2 (rather than 30 kg/m^2), respectively (55). In the absence of established diagnostic criteria for rheumatoid cachexia, the prevalence of the syndrome ranges from 8% to 67% in the RA population (17), however, it has been suggested that RA patients that experience these detrimental body composition changes may have worse functional ability and disease symptoms as well as increased risk for CVD (1, 56). Blocking TNFα, via anti-TNFα medication, does not reverse rheumatoid cachexia up to a period of six months in either early or established RA patients (57, 58). However, exercise is an intervention that can significantly reverse these phenomena, by significantly increasing muscle mass with no adverse effects (15).

A summary of the mechanisms by which physical activity can improve disease-related and systemic manifestations in RA is shown in Figure 1.

Figure 1. Overall mechanisms of the beneficial effects of physical activity and exercise on disease-related and systemic manifestations in RA



Exercise-induced IGF expression increases muscle mass via the mTOR pathway, thus, inhibiting muscle wasting and rheumatoid cachexia. The interaction of NFAT and the glycogen-p38 mitogen activated protein kinase regulates the expression of intramuscular IL-6, which in turn triggers hepatic glucogenolysis and lipolysis and coincides with a) inhibition of inflammatory cytokines (TNFa and IL-1) and b) stimulation of anti-inflammatory cytokines (IL1-ra, IL-10, sTNFr). Exercise also improves the cardiovascular profile via increases in the long-term expression of GLUT4 (reduction in insulin resistance), NO (improved vascular function), HDL and reductions in oxLDL (improved lipid profiling). Improvements in VO2max, as a result of increasing exercise, result in significant reductions in fatigue.

Abbreviations: GLUT4: Glucose transporter type 4, HDL: high density lipoprotein, oxLDL: oxidized low density lipoprotein, NO: nitric oxide, VO2max: maximal oxygen uptake, MAPK: mitogen-activated protein kinase, Ca^{2+}: calcium, NFAT: nuclear factor of activated T-cells, mRNA: messenger RNA, IL: interleukin, sTNFr: soluble tumour necrosis factor receptor, IL-1ra: interleukin 1 receptor antagonist, TNFa: tumour necrosis factor alpha, IGF: insulin growth factor, mTOR: mammalian target of rapamycin.

3.0 Barriers for physical activity implementation in clinical practice

Despite the well-documented benefits of physical activity and exercise on various different physiological mechanisms that can significantly ameliorate disease symptoms and improve the overall function and quality of life in RA (59), the physical activity and fitness levels of patients with RA remain significantly lower compared to the general population. The QUEST-RA study that investigated physical activity levels in RA patients from 58 sites in 21 countries revealed that only 13.8% of RA patients perform physical activity more than three times per week, i.e. the currently recommended levels (60).

Given the multiple different benefits of physical activity in RA, studies have focused on identifying the different barriers that may hinder participation. The most recent systematic review in this field reveals that RA patients report as barriers factors that overlap with those observed in the general population, such as lack of time and cost (34). However, the majority of studies identify also disease-specific barriers particularly pain, fatigue and functional disability (34), all of which, interestingly and as already mentioned, can be significantly improved once patients start exercising (6, 10).

The lack of physical activity and exercise in the RA population may also be due to other factors, predominantly influenced by rheumatology healthcare professionals. Until recently, the diagnosis of RA was accompanied by the advice to rest and avoid physical activity, as healthcare professionals feared that exercise may exacerbate disease symptoms and lead to further functional disability. Despite the overwhelming evidence that physical activity, even high-intensity exercise, is safe in RA and has no adverse effects, implementation of programmes aiming to enhance physical activity in routine clinical practice is still lacking. In line with this, RA patients report as a main barrier for their reduced participation in physical activity, the lack of advice and support from their managing rheumatology healthcare practitioners. This is confirmed by a recent review on barriers and facilitators for physical activity in RA as well as the most recent qualitative studies on physical activity engagement in RA (34, 61, 62).

4.0 How can we implement physical activity advice in clinical practice

As described above, there is convincing data at present to suggest that increasing physical activity can improve disease outcomes in RA, thus leading to better disease management. It is expected, therefore, that attempts would be made in the last decade to help implement programmes aiming to improve physical activity as integral parts of the overall management of RA, or at least that physical activity is promoted more actively within clinical practice. However, this is not the case.

Several studies have addressed possible ways to help patients become and remain more physically active (63, 64). Irrespective of the outcomes of these studies, the long-term engagement in physical activity significantly suffers after the end of any intervention, as patients that previously engage with physical activity and/or exercise tend to become again physically inactive post intervention, which is general phenomenon in other non-communicable diseases (65). To address this important matter, we propose a theory for implementation that can effectively address key barriers from both (a) the healthcare practitioners' and (b) the patients' perspectives in order to increase levels of physical activity; this is also based on the well- and long-known relationship between the managing rheumatology healthcare practitioner and the patient, a keystone in healthcare, which evidently promotes uptake and adherence to behaviors that can significantly improve health (66, 67). It is however important to note, that this implementation model, although theory and evidence-based, remains to be appropriately tested in relevant trials as a whole or in part.

4.1 Addressing healthcare practitioners' barriers for implementing physical activity in clinical practice

At present, unfortunately, we and others have shown that there is a lack of provision from official bodies – such as the British Society of Rheumatology, EULAR, Arthritis Research UK and others – on physical activity advice for RA patients, as well as advice to healthcare professionals and commissioners on how to effectively: (a) incorporate physical activity in the clinical management of RA and (b) promote long-term adherence to a physically active lifestyle (68, 69). As such, even if individual attempts to promote and implement physical activity in clinical practice existed, the material to support such initiatives (e.g. instruction on how to implement or how to address patient's aims in an individualized manner) are non-existent for RA. This is surprising, since embedding physical activity into healthcare streams and promoting long-term adherence are now recognized priority targets by the World Health Organization (WHO) for the effective management of non-communicable chronic diseases, such as RA (70). The WHO has proposed that physical activity implementation can be achieved with capacity building at the level of frontline healthcare practitioners managing the patients (i.e. in the case of RA, rheumatologist healthcare professionals) (71). Unfortunately, a very low number of doctors involved in the management of RA (17%) have the confidence to prescribe physical activity for their patients (72), a fact revealing that relevant provision is probably necessary at all levels of a rheumatologist's professional career, from undergraduate, through postgraduate training, to specialization and continuing professional development. In addition to that, information on physical activity, even when provided by the consulting doctors, is inconsistent at present, and there is uncertainty about how to advise RA patients on increasing physical activity (73) which, as previously stated, is an important barrier for the patients (62).

For a wider implementation and scaling-up of physical activity engagement within the healthcare set-up, we propose that this should be led by the main healthcare practitioners involved in the patient's management during routine clinical visits, in a repetitive, enabling and reinforcing fashion. Education about the mechanisms and benefits of physical activity on different health parameters is not covered extensively in the curricula of Medical Degree programs (74) and even less afterwards. Therefore, while "deep infrastructure" is developed at all levels/stages of a health practitioner's career, perhaps a viable interim solution to address this problem could be expert-led e-educational capacity-building initiatives. E-learning education is a preferable method of learning for healthcare practitioners while collective evidence reveals that it can facilitate wider dissemination and up-scaling of successful practices (75). Capacity building of frontline healthcare professionals for incorporating physical activity in clinical practice is also in line with recent recommendations from the WHO and other national authorities, for optimizing healthcare in a sustainable manner (70). Considering the financial pressures on National Health Services, physical activity implementation should also be cost–effective, so potentially the inclusion of brief but meaningful physical activity advice during routine patient visits (i.e. a pragmatic approach), may be an intervention that holds great promise (76), but this needs to be prospectively evaluated in RA.

The above suggestion, is also supported by good quality evidence. Strong evidence has emerged from other disease entities that when healthcare practitioners incorporate physical activity advice in their clinical practice, they can significantly contribute towards altering behaviors and help patients with other chronic non-communicable diseases to become more physically active. Specifically, when clinicians in primary care were trained to deliver brief (3-4 minutes) interventions during routine patient visits, this resulted in increased levels of physical activity over a 2-year follow-up as well as significant improvements in cardiorespiratory fitness (77). In addition, the PREMIER and SMARTER trials (78, 79) provided strong evidence that brief lifestyle and physical activity counselling among adults with prehypertension or stage 1 hypertension and/or diabetes [both highly prevalent in RA (80-82)] resulted in a significant reduction in cardiovascular risk with excellent sustainability. These results are also in line with research in RA. A randomized controlled trial investigating the effects of patient education about the benefits of improving lifestyle vs. standard care, demonstrated that the intentions and behaviors of the RA patients change beneficially, and importantly this can significantly reduce blood pressure, while such changes were not observed in the control group (83). Brief (3-4 minutes) healthcare practitioner-led advice on physical activity during routine patient visits (a) using specific guidelines and current national recommendations (76, 84) and after (b) adequate expert-developed e-Learning capacity building, could therefore help overcome one of the most important barriers within clinical practice, in order to address the lack of physical activity implementation in the clinical care of RA.

4.2 Addressing patients' barriers for a sustainable increase in physical activity

Incorporating advice about physical activity and reinforcing its importance with viable targets during routine clinical visits, therefore, is the first key step. In line with this, several different lines of evidence reveal that physical activity as part of the management of RA is very rarely discussed in routine face-to-face rheumatologist-patient visits (72) and the time allocated for such a discussion remains inadequate. Therefore, it is not surprising that RA patients still identify the lack of clarity and support for physical activity from their physicians/nurses as a main barrier to their participation (85). In contrast, receiving such information has been shown – in early qualitative studies - to associate with higher levels of physical activity engagement among RA patients (86). Moreover, a recent qualitative study revealed that patients require physical activity advice from their "trusted health professionals" in order to become more physically active but most importantly, to adhere to such a lifestyle (61, 62).

In addition to the above, empowerment for RA patients from trusted healthcare professionals to develop their knowledge about the safety and effectiveness of physical activity is key, particularly to understand that their own main barriers – i.e. fear of exacerbating symptoms such as pain and fatigue and further worsening functional ability – can be significantly improved by exercising. Thus, if our first proposed step for the capacity building of healthcare professionals doesn't take place, the improvement in knowledge/education of the patients about the beneficial mechanisms of physical activity in RA may be inadequate, the response effectiveness will lack specificity, thus, compromising long-term sustainability of the beneficial effects of physical activity.

Importantly, another key factor to support a sustainable increase in physical activity in RA is via disruptive social innovation i.e. the empowerment of the communities (patient organizations, community groups, third sector, exercise professionals) to support either (a) physical activity referrals from healthcare practitioners or even (b) implement physical activity interventions for RA patients on their own. Capacity building of exercise professionals, patient volunteers and/or third sector organizations, via development of relevant workshops and seminars, in order to help them develop their knowledge on how to exercise RA patients is key for a sustainable implementation. For example, when exercise coaches and volunteers know how to develop individualized and safe exercise interventions for RA patients, which are incentivized and formally rewarded, while at the same time offering a range of activities (e.g. dance, water-based activities, modified sports such as walking football, tai-chi etc.), is also an important factor for developing sustainable physical activity interventions. In the United States, a similar approach exists with the "exercise pharmacies" for patients with CVD, whereby healthcare professionals confidently refer patients with CVD to exercise professionals / community-build programs to improve their health outcomes (87). In such a way, RA patients can attend disease-specific physical activity RA referral schemes with a variation of physical activities which may further contribute to long-term sustainability. It is important to note, that this approach, addresses established patient-identified barriers for reduced physical activity and specifically the lack of: (a) RA specific physical activity programs and (b) knowledgeable exercise instructors (34).

4.3 Physical activity advice in clinical practice and referral process

A schematic representation of our healthcare practitioner-led implementation suggestion for the long-term sustainability of physical activity appears in Figure 2.

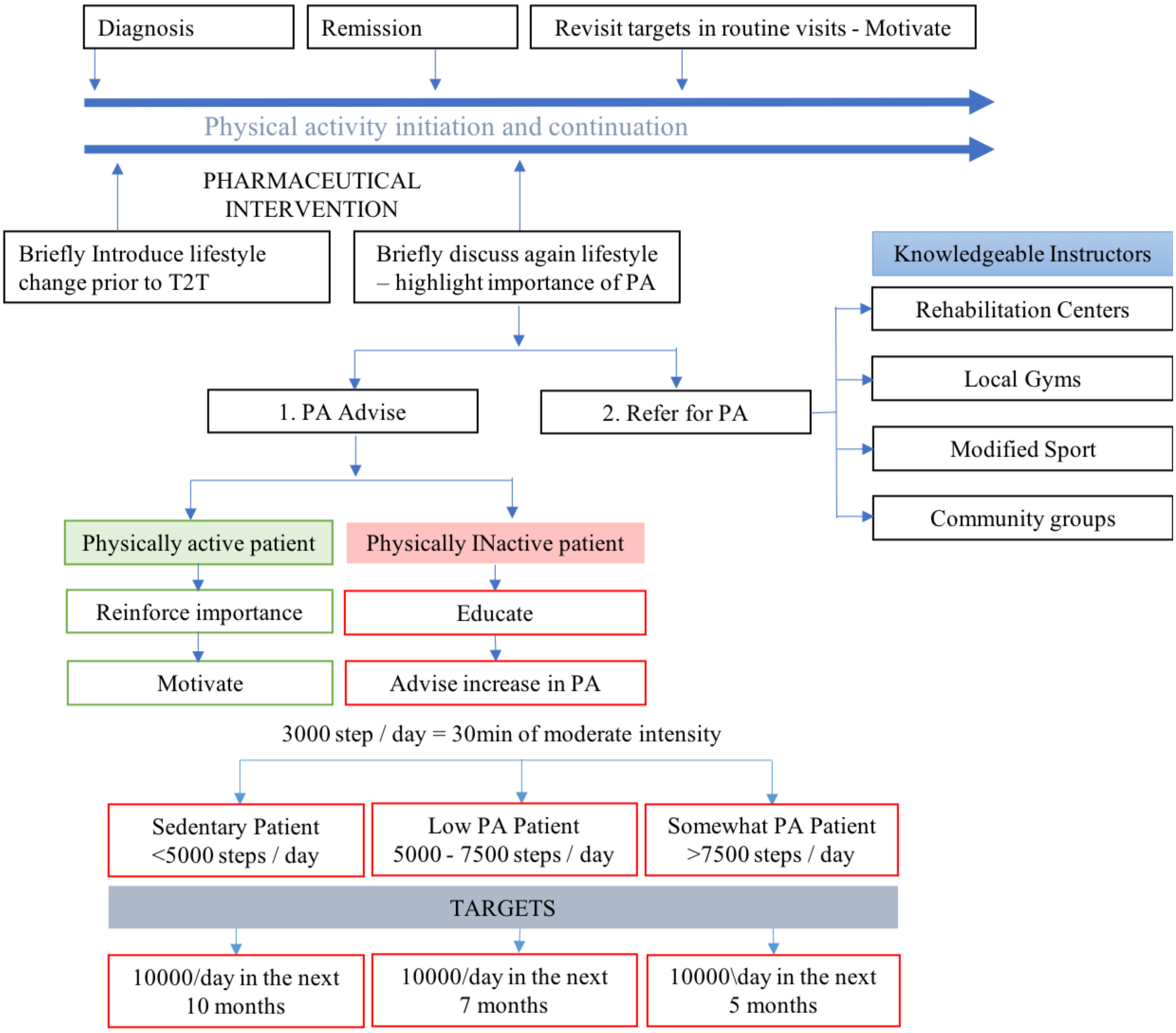
Step 1: Patients with early RA or those with-long standing RA are currently best treated with a treat-to-target approach, based predominantly, if not exclusively, to semi-objective assessment of their disease activity. Irrespective of their current disease status, and alongside any decisions about the best possible pharmacological management, patients should be informed briefly during their routine visits, that implementing appropriate lifestyle modifications, including becoming more physically active, is also important and will be needed for effective long-term management. This first introduction of the role of physical activity should be consistently re-inforced by all rheumatology health professionals in every subsequent visit. Once the inflammatory component of the disease is sufficiently controlled, patients should be motivated to engage in physical activity with specific targets agreed with them (e.g. increase steps / week, see Figure 2). A first viable and easy way to achieve this is by increasing walking time, a mode that improves significantly health outcomes (88). Current suggestions for public health suggest walking 10.000 step / day, with 3.000 step / day equating to approximately 30 min of moderate physical activity (89). As a first step to increase physical activity, this information can briefly be provided/prescribed within clinical practice by the managing rheumatologist and re-inforced consistently by all members of the rheumatology multidisciplinary care team. Altrnatively, based on their current physical activity levels (minutes or steps / week), physically inactive patients should be motivated to progressively reach the recommended levels of physical activity levels equating to 150 minutes / week (rather than step / day, as per the previous example). Targets to reach the recommended physical activity should be based on current levels and be re-visited and revised in every routine patient visit. Not achieving previously agreed targets should be briefly discussed, and healthcare professionals should try to further motivate patients to reach their targets by their next routine visit. However, it is important to note that the current established public health recommendations suggest 150 min / week of moderate to vigorous physical activity, combined with resistance training twice a week. Implementation of these recommendations, is likely to exceed the knowledge, competence and even time-availability of rheumatology healthcare professionals, so once step targets are reached, onwards referral to exercise physiologists could be considered.

Step 2: Empowerment of RA patients to understand that physical activity is key for their long-term management is also necessary. This advice can also be brief and should always be accompanied by ensuring patients, that physical activity is (a) safe and (b) can improve the main RA symptoms that may currently inhibit their participation in physical activity (i.e. functional disability, pain and fatigue).

In addition to the above approach, patient-centered approaches could also facilitate implementation. Such an initiative has been developed recently by the most prominent organization for RA patients in the UK, the National Rheumatoid Arthritis Society (NRAS). This is a freely available online interactive e-program developed by patients themselves, facilitated by experts, and aims to help RA patients set specific goals in order to self-manage risks related to their condition as well as mitigate their CVD risk (e.g. adherence to medication, increasing physical activity and improving diet). The program is firmly based on research work that has been progressively developed over many years by a collaboration of patients, rheumatology health professionals, exercise physiologists, behavioural scientists and educationalists aiming to implement lifestyle interventions to reduce CVD risk in peiople with RA (77). However, its effectiveness and reach remain to be formally evaluated.

Step 3: Capacity building of communities (e.g. exercise and sports coaches, patient volunteers, exercise instructors in local gyms) that can support physical activity is also necessary, albeit this is a public health rather a healthcare matter. Developing knowledge on how to exercise people with RA and incentivizing physical activity professionals (gym instructors, sports coaches, physical activity community groups) with relevant awards, will help develop a body of professionals that will be able to help RA patients exercise safely and progressively in order to achieve improvements in disease symptoms as well as overall health benefits. The purpose of these initiatives, which has to be reinforced by the managing healthcare practitioners during routine visits, has to be the aforementioned specific recommended targets of 150 min /week (moderate to vigorous intensity with the addition of resistance training) in order to optimize the healthcare management of RA patients. A single, clear, simple and consistent message reinforced by all involved in an RA patient’s care pathway (from community to primary and secondary care and beyond) is essential for future change.

Figure 2: Healthcare practitioner-led model for the implementation of physical activity



This proposed approach should be followed consistently by all members of the multidisciplinary care team and the targets should be consistently stated by all rheumatology healthcare professionals in routine clinical practise. Abbreviations: T2T = treat to target, PA = physical activity.

Summary

Increasing physical activity and/or exercise can beneficially and simultaneously impact beneficially on different disease-related symptoms and systemic manifestations of RA. However, implementing physical activity in routine practice has always been a challenge for healthcare practitioners due to unfounded patient-specific barriers, lack of understanding or misconceptions of health practitioners as well as lack of relevant infrastructure and provision. Implementation of physical activity in clinical practice can be led, in a pragmatic manner, by rheumatology healthcare practitioners during routine patient visits and supported by social innovation. The main constituents of an implementation model are proposed based on current evidence and expert opinion, but its effectiveness and cost-effectiveness should be tested in appropriately designed trials.

Research Agenda

- More methodologically robust studies are required to understand the effects of physical activity on different physiological mechanisms in RA, including inflammatory, cardiac and inflammatory responses
- Research is currently required to better undertstand how to implement physical activity in clinical rac tice, given the multiple beneficial effects of physical activity on RA clinically- and patient-important outcomes

Confict of interests statement

The authors disclose that they do not have any conficts of interest

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